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Invited Editorial

Classical Clinical Genetics in the Era of Molecular Genetics

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Medicine is undergoing a quiet revolution. Molecular genetics is transforming clinical science and practice; the development of the Human Genome Project allows new methods of disease identification and of predicting disease patterns for individual patients. Knowledge of the human genome will deepen our understanding of pathological processes and may lead to prevention or effective therapy of currently not treatable diseases [Fulginiti, 1993].

No wonder that most clinical geneticists as well as pediatricians, obstetricians, and pathologists with an interest in cytogenetics, syndromology, and genetic epidemiology are enthusiastic about the new methods and perspectives and have committed themselves to molecular genetics. A parallel trend is observed in the leading journals in this field: In most of the genetic periodicals DNA studies have gained ascendancy over clinical, epidemiological, and family investigations applying nonmolecular methods, methods which have almost disappeared from some of the leading genetic journals characterizing themselves as "human," "medical," or "clinical" in their titles (the exception of the *American Journal of Medical Genetics* only proves the rule). It is by no means surprising that the training of students has also been adapted to this development. In the curriculum of most medical faculties the limited amount of genetic instruction is devoted more and more to molecular methods rather than classical genetics and it is still a general complaint that this limited time does not suffice to teach even the rudiments of up-to-date techniques and principles.

This progress in molecular genetics undoubtedly is a beneficient advance. However, its overestimation and the neglect of classical methods of clinical genetics will result in adverse effects. Most importantly this will affect the adequate evaluation of the clinical picture, i.e., the phenotype. This may lead to incorrect selection of patients for more sophisticated and often wasteful investigations with immense expenses, whereas patients and families in urgent need of molecular analyses may miss the necessary investigations.

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This is a serious problem in Hungary, and probably in many other countries where facilities for clinical genetics are modest, and where, because of various reasons systematic instruction in genetics in medical schools began only recently. Here we have a few enthusiastic but overtaxed clinicians in their 50s or 60s who learned pedigree and phenotype analysis, cytogenetics, and elements of genetic epidemiology mostly through personal initiative 20 or 30 years ago (but who understand little of genes) and a pleasurably growing number of young research fellows (including physicians) who are very skillful in Southern blot, polymerase chain reaction (PCR), etc. techniques, but are less familiar with the traditional methods including physical examination of the patient.

This situation causes much inconvenience as demonstrated by the Hungarian Congenital Malformation Registry organized by Czeizel [1988] in 1962. Notification of congenital anomalies was then made compulsory and for about 2 decades the system functioned with high efficiency: Of the expected 60 of 1,000 total births, on the average 47 of 1,000 congenital anomalies were registered (78%). Follow-up of these cases showed a high degree of reliability which was largely due to the skills and diagnostic acumen of the reporting physicians (mainly pediatricians). This served as the basis for a series of renowned epidemiological and teratological studies. Unfortunately, efficiency (43%) and reliability have declined considerably during the last few years [Annual Reports, 1993, 1994]. This is a multicausal event but decreasing interest and competence certainly contributed to these adverse changes.

Similar conclusions can be drawn from another perspective. In 2 earlier studies we found that after appropriate instruction, neonatologists and obstetricians of our region reached a recognition rate of autosomal trisomy syndromes that was compatible with the figures of cytogenetic mass screenings [Méhes, 1973; Méhes and Bajnóczky, 1990]. While there was a remarkable advance in pre- and perinatal care, while routine gene diagnosis became available on a few diseases, the diagnostic vigilance and accuracy of clinically recognizable autosomal aberrations deteriorated: Only a part of the expected cases was discovered during the last 5 years in the same region. Thus, for example, the birth prevalence of trisomy 18 sank from the original 1 in 8,600 to

1 in 20,570. No other possible causes such as increasing number of terminations after prenatal diagnoses or alterations in maternal age could be detected as an explanation of the changes.

Without referring to further examples from Hungary, I assume that the hazards of isolating the patient from the examiner of his or her molecules have also been recognized in other parts of the world. The fact that in some countries "medical genetics can now speak with a new voice—as a member of the organized establishment of medicine" [Epstein, 1992] is welcome, provided that this speciality will not exclusively mean an activity of laboratory experts who do not see or care for or about the patient. It should be kept in mind that depending on the individual problem, old and new methods may be equally or alternatively important. Old methods are by far not obsolete. The simple pedigree analysis is still the basic aid to establish the type of inheritance. Familial occurrence of renal calcium stones had been known for centuries but quite astonishingly only recent family investigations revealed the autosomal dominant transmission of the renal form of "idiopathic" hypercalciuria [Harangi and Méhes, 1993]. Phenotype analysis and syndromology are indispensable in clinical genetics [Hall, 1993]. Only physicians capable of recognizing the difference between normal and abnormal structure and skilled in the evaluation of major and minor anomalies can be successful in syndrome identification. Congenital anomalies may also call attention to several inborn errors of metabolism, although in these cases the minor morphological aberrations are secondary phenomena arising after organogenesis. Minor anomalies and variants can be suggestive of the prenatal origin of the associated disorder [Méhes, 1988; Merlob, 1994], thus their simple and inexpensive investigation may be useful, e.g., in cancer research [Hecht, 1987]. Case-control studies are constantly needed in identifying human teratogens [Holmes et al., 1987; Friedman, 1992]. The physical findings supplemented with those of imaging procedures, metabolic, and psychological tests are essential in genotype-phenotype correlation studies [Rosenstein, 1994]. Cytogenetics with its breakpoint analysis is an important approach to gene localization. However, even traditional, nonbanded chromosome preparations may still be useful in recognizing hitherto overlooked phenomena. In a retrospective analysis of old slides of patients with Fanconi-anemia and ataxia-teleangiectasia we have just found that premature centromere division of the acrocentrics may be a manifestation of chromosome instability [Méhes and Bühler, 1995]. Classical methods of epidemiology occasionally combined with linkage studies are still necessary and can often be regarded as screening for "molecular epidemiology" [Morton, 1993]. Trials on preventive measures are also frequently based on an epidemiological approach [Czeizel, 1993].

All this means that the importance of the various methods in the classical approach to genetic diseases has by no means diminished and clinical genetics must remain a medical discipline even in the era of molecular genetics. I fully agree with the statement that "molecular diagnosis is only one part of a battery of tests in which clinical suspicion and your own clinical expertise are the basis of most diagnoses" [Surh, 1994].

If so, efforts should be continued and increased to educate the community and the somewhat reserved medical community in molecular genetics. We urgently need physicians, dentists, nurses, and all other health professionals who are aware of the necessity of gene diagnosis and of possible gene therapy. Our educational system must adapt to the revolutionary new scientific and medical environment [Fulginiti, 1993]. At the same time, unflagging emphasis in training of classical family investigation, phenotype analysis, syndromology, cytogenetics, and other traditional methods in medical genetics seems to be critical in producing well-balanced clinical geneticists. A year ago I pleaded for this principle in Hungary [Méhes, 1994] where the neglect of classical methods in the training of medical students and PhD fellows is beginning to lead to one-sidedness and all of its consequences in the practice of medical genetics. Since "genetics leaves no bones unturned" [Debenham, 1994] I hope that a professional and a scientific career will also be guaranteed for those who are interested "only" in classical clinical genetics and that the importance of subdisciplines not fashionable nowadays will be acknowledged before it is too late in Hungary. And hopefully not in this country alone.

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